**Supplementary Methods**

**Anti tumour experiments**

All animal experiments were performed to the according to the local regulations Home Office UK; Direction des Services Vétérinaires, Ministère de l'Agriculture et de la Pêche, France and in USA an AAALAC-accredited facilities. U87-MG cells (5x106  cells in MEM serum free medium) were implanted in the flank of female nude mice (nu/nu:Alpk) (AstraZeneca, Alderley Park, UK) between the ages of 8 and 12 weeks.

LuCAP E86 (Vessella) tumour fragments (approximately 40 mm3) from donor animals were aseptically implanted subcutaneously in the flank of male SCID (AstraZeneca, Alderley Park, UK) mice between the ages of 8 and 12 weeks.

C4.2 LnCAP in vivo experiments were performed under contract by Oncodesign, 20, rue Jean Mazen, 21076 Dijon Cedex, France.

LnCap‑C4.2 (1x107 cells in RPMI serum free medium mixed 50 :50 with Matrigel™) into the right flank of male CB17-SCID mice (Charles River, France). LnCaP‑C4.2 tumor cell implantation was performed 24-72 hours after a whole body irradiation with a γ-source (1.44 Gy, 60Co, BioMep, Bretenières, France).

CTG-824 in vivo experiments were perfomed under contract by Champions, Oncology, Inc., 855 N. Wolfe Street, Suite 619, Baltimore, MD 21205, USA. Tumour fragments (approximately 40 mm3) from donor animals were aseptically implanted subcutaneously in the flank of female immunocompromised mice (Taconic; NCr nude) between 5-8 weeks of age.

Once tumours reached ~200-500mm3 animals were randomized into control and treatment groups. Tumour volume was calculated twice weekly from bilateral caliper measurements using the formula (Length x width x width) x π/6). AZD8186 was generally formulated once weekly as a suspension in 0.5% HPMC/0.1% Tween™ 80 and dosed once or twice daily (0 and 6-8 hours). Vistusertib was formulated as a suspension in in 0.5% HPMC/0.1% Tween™ 80. For combination dosing AZD8186 and vistusertib were co-formulated in 0.5% HPMC/0.1% Tween™. Growth inhibition from the start of treatment was assessed by comparison of the geometric mean change in tumour volume for the control and treated groups. Statistical significance was evaluated using a one-tailed, two-sample t-test of unequal variance.